AWARD NUMBER: W81XWH-14-1-0622

TITLE:

Assessment of MRI-Based Marker of Dopaminergic Integrity as a Biological Indicator of Gulf War Illness

PRINCIPAL INVESTIGATOR: Deborah M. Little PhD

CONTRACTING ORGANIZATION: Scott and White Memorial Hospital
Temple, TX 76504

REPORT DATE: October 2015

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2015	Annual	29 Sep 2014 – 28 Sept 2015

4. TITLE AND SUBTITLE

Assessment of MRI-Based Marker of Dopaminergic Integrity as a Biological Indicator of Gulf War Illness

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-14-1-0622

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Deborah M. Little PhD

E-Mail: delittle@sw.org

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Scott & White Memorial Hospital
2401 S 31ST ST
Temple TX 76504-7115

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Gulf War illness (GWI) is characterized symptomatically in veterans who served in the 1990-1991 Gulf War by a constellation of symptoms including headache, pain, fatigue, gastrointestinal problems and alterations in cognition. Diagnostic tests and effective treatments have not been identified. The proposed project leverages existing brain imaging data from a sample of 1990-91 Gulf War veterans and includes an in-depth, detailed analysis of the integrity of the corticostriatal circuit using high resolution diffusion imaging. While institutional human subjects approvals have been obtained during this period, there is no other progress to date under this award as the start of this project is pending initiation of the parent study which has been delayed due to DMDC regulation changes and delays in institutional contracting which are detailed in the annual reports for the parent grant. The revised timeline for the parent study has a data collection start date in the first quarter of 2016. Consistent with this delayed start, no funds have been used to date.

15. SUBJECT TERMS

Gulf war illness; magnetic resonance imaging; dopamine; diffusion tensor imaging

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	7	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Table of Contents

1. Introduction

Gulf War illness (GWI) is characterized symptomatically in veterans who served in the 1990-1991 Gulf War by a constellation of health symptoms that typically include some combination of persistent headache, widespread pain, fatigue, gastrointestinal problems and alterations in cognitive function. Diagnostic tests and broadly effective treatments have not been identified for GWI. Although there are multiple indications of significant central nervous system differences between GWI cases and controls, there is still no comprehensive understanding of the spectrum of alterations in cerebral neurobiology/neurophysiology and how they result in GWI symptoms. One understudied area of research is the role of the corticostriatal circuit. Multiple studies have demonstrated preliminary indications of neuronal dysfunction in this circuit (1, 2) but these are limited in scope and in the characterization of the symptoms. This project will leverage existing brain imaging data from a well-characterized sample of 1990-91 Gulf War veterans to assess brain structures and processes of high interest for understanding GWI (CDMRP funded, PI: L. Steele), but not previously studied in ill Gulf War veterans. Our aims are to assess the integrity of the substantia nigra, basal ganglia and cortex as markers of integrity of the nigro-striatal dopaminergic pathway using high resolution diffusion tensor imaging (DTI) in 80 veterans with GWI and 50 healthy Gulf War veteran controls and to characterize the etiological and clinical correlates of alterations in brainstem and basal ganglia integrity. If successful, this study will form the foundation for novel approaches to clinical intervention to include specific targeting of the dopaminergic system.

2. Keywords

Gulf war illness; Corticostriatal circuit; Nigro-striatal circuit; Dopamine; Diffusion tensor imaging; Magnetic resonance imaging

3. Accomplishments

As administrative background, the grant described in this progress report supports the secondary analyses of data collected under the CDMRP funded grant "Assessment of diverse biological indicators in Gulf War Illness: Are they replicable? Are they related?" (W81XWH-11-1-0812; PI: Lea Steele). W81XWH-11-1-0812 "Assessment of diverse biological indicators in Gulf War Illness: Are they replicable? Are they related?" will be referred to as the "parent" grant (**parent**) throughout. The parent is a multi-site study with the responsible institution being Baylor University. The data collection site for the parent is Scott and White Memorial Hospital.

For the project summarized in this annual report, there are also two study sites with the primary being Scott and White Memorial Hospital and the secondary site being Baylor University.

The parent study has not yet begun data collection due to a number of significant delays involving access to DMDC data as well as three changes in the secondary site for imaging data. As such, and as has been communicated to program staff, we have not begun this secondary analysis grant.

In order to carry out the research in the parent grant, the parent grant PI, has recently accepted employment at Baylor College of Medicine. This change will affect all parent IRBs and regulatory for this secondary project. This annual review reflects these delays in the parent grant. Again, no funds on this secondary grant will be used until all new regulatory has been completed for the parent grant. Following this, we will revise all regulatory for this project to include final HRPO approvals.

What were the major goals of the project?

Major goals of the project are identified as the major tasks as described in the approved statement of work. For this contract, there are 7 major goals which fall into the general categories of regulatory, quality assurance of data quality, quality assurance of staff for the required imaging analysis, and development and validation of methods. These are outlined below as well as a statement of degree of completion.

Task 1. Human Subjects Initial Approval and Review (months 1-4):

This task had x specific steps. These included a revision to the parent grant IRB at Baylor University to provide the research participants the ability to specifically allow secondary analysis of the imaging data. Following this approval, the secondary site (for the parent) was also revised and approved. HRPO also approved the revisions necessary to the parent grant to allow secondary data analysis. Following these approvals, the IRB for this project was submitted to the prime institution and following approval, submitted to the secondary site. Shortly after these approvals the PI of the parent site indicated a plan to change employment. As such, this Task will now require the parent grant to obtain IRB approval at the new parent institution, and will require revisions to the IRBs for this project.

Action plan, Task 1.
(1) Baylor College of Medicine approval for the parent study
(2) Approval of a revised IRB for this specific contract at the primary institution of record (Scott and White Memorial Hospital)
(3) Approval of this contract IRB at the second study site (Baylor College of Medicine); and finally,
(4) Submission to HRPO

Task 2. Quality assurance protocol and data collection (1-24):
No progress to date.

Task 3. Training of staff on image preprocessing (months 1-5)
No progress to date.

Task 4. Methods development and validation for Substantia Nigra characterization (training data analyst on region of interest placement) (Aim 1)
No progress to date.

Task 5. Methods development and validation for thalamic nuclei assessment (training data analyst on seed voxel placement) (Aim 2)
No progress to date.

Task 6. Methods development and validation for regions to be extracted via normalized masks (putamen, caudate, cortex) (Aim 3)
No progress to date.

Task 7. Data Analysis
No progress to date.

What was accomplished under these goals?

All approvals prior to HRPO were obtained at which point the parent grant PI notified the PI of this grant of a change in employment which will require additional IRB approvals prior to HRPO submission.

What opportunities for training and professional development has the project provided?

Using institutional support, the PI travelled to Boston to meet with a major Gulf War Illness consortium study staff. This meeting had the intention to ensure sufficient overlap in imaging methods to allow leveraging of imaging data to be collected for the consortium.

How were the results disseminated to communities of interest?

No data has been collected for the parent grant resulting in no data analysis for this project. As such, there are no results to disseminate.

What do you plan to do during the next reporting period to accomplish the goals?

1. The primary task will be to facilitate all necessary IRB approvals. We will submit applications with the request of provisional approval pending parent grant IRB approvals. This will allow us to amend the applications as soon as those approvals are in place reducing the total time for approvals.
2. Additionally, the PI will continue to work with program staff to revise timelines and budgets to facilitate progress as soon as the IRBs are in place.

4. Impact

What was the impact on the development of the principal discipline(s) of the project?

Data analysis has not yet begun. As such, there is nothing to report.

What was the impact on other disciplines?

Data analysis has not yet begun. As such, there is nothing to report.

What was the impact on technology transfer?

Data analysis has not yet begun. As such, there is nothing to report.

What was the impact on society beyond science and technology?

Data analysis has not yet begun. As such, there is nothing to report.

5. Changes/Problems

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

This project is, at present, 8 months behind schedule. These delays are due to delays in data collection for the parent grant and due to additional human subjects approvals associated with a change in employment for the PI of the parent grant.

As described in Task 1, efforts will be focused on reducing the timeline for new regulatory approvals associated with changes in the parent grant. As soon as these approvals are in place and data analysis on the parent grant is begun we will work with program staff to revise the timeline and budget to speed completion of the goals and tasks associated with this project.

Changes that had a significant impact on expenditures

No funds will be used until data collection for the parent grant has begun and revised timelines, budget period, and all other approvals from program staff are in place.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals.

Not applicable as no vertebrate animals are included in the scope of work.

Significant changes in use of biohazards and/or select agents

Not applicable as no biohazards and no select agents are included in the scope of work.

6. **Products**

Data analysis of imaging data collected in the parent grant have not begun. As such, there are no products to report.

7. **Participants & Other Collaborating Organizations**
What individuals have worked on the project?

No budgeted effort has been used for this project and will not until data collection for the parent grant has begun. As such, there is nothing to report.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

What other organizations were involved as partners?

This project currently involves Scott and White Memorial Hospital as the prime and Baylor University as a subcontract. The Co-I, Lea Steele, at Baylor University has resigned from her position at Baylor University and has accepted employment at Baylor College of Medicine. As such, we will request permission from program staff to remove Baylor University as a study site and will request permission to add Baylor College of Medicine.

8. **Special Reporting Requirements**

Nothing to report.

9. **Appendices**

No appendices are included.

10. References Cited in this Report

1. Haley RW, *et al.* (2000) Effect of basal ganglia injury on central dopamine activity in Gulf War syndrome: correlation of proton magnetic resonance spectroscopy and plasma homovanillic acid levels. *Arch Neurol* 57(9):1280-1285.
2. Haley RW, *et al.* (2000) Brain abnormalities in Gulf War syndrome: evaluation with 1H MR spectroscopy. *Radiology* 215(3):807-817.